Remarks/Arguments

Status of Claims

Claims 1-3, 5 and 7-9, drawn to nucleic acid sequences encoding human vanilloid receptor-like (VRL) receptor, an expression vector comprising a nucleic acid which encodes a VRL, host cells comprising the vectors disclosed and claimed in the instant application and a method of producing VRL receptor polypeptide are pending and under examination. Claims 4, 6, and 10-17 have been canceled.

Amendment(s) to the Specification

Specification Amendment(s)

In order to more completely conform with the statutory requirements which establish the requisite format and components of an application, the specification of the instant disclosure has been amended. More specifically, the application has been amended to:

1. Include a section heading indicating where the "Brief Description of the Drawings" begin,
2. to include a section heading indicating where the "Detailed Description" begins, and
3. to amend the descriptions of Figure 2 and 3 to correspond to the labels provided on the replacement sheets. No new matter has been added by virtue of these changes.

The Office Action also indicates that the instant application "contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2)" (Office Action, page 3) and that such sequences require a sequence identifier in the form of SEQ ID NO: X. The Action indicates that appropriate correction is required.

Applicants traverse this point. Applicants acknowledge that the instant specification includes nucleotide and amino acid sequences that are encompassed by the provisions of 37 CFR 1.821. Applicants respectfully direct the Examiner's attention to the fact that the nucleotide and amino acid sequences disclosed and claimed in the instant application have been assigned sequence designations of the requisite format. For example, the Examiner's attention is directed to page 1 of the application, lines 22 to 28, which corresponds to the "Brief Description of the Drawings" section of the application. All of the sequences disclosed in the application are referred to by sequence identifiers that are assigned in this section of the application. Further support comes from the observation that the sequences are consistently referred to by their SEQ ID NOS. For example, see page 2, lines 3 to 8 and page 12, lines 1-11. Accordingly, Applicants are of the opinion that the text of the specification as complies with the statutory requirements.

Applicants respectfully request reconsideration of the application in view of the foregoing explanations and amendments of the claims and specification and in light of the following remarks and reasoning.

Amendment(s) to the Drawings

The Notice of Draftperson's Patent Drawing Review (PTO-948) indicates that the drawings filed on December 8, 1999 are objected to under the provisions of 37 CFR 1.84 and that indicated objection will not be held in abeyance.

The Notice indicates that the drawings are not in compliance with the requirements of 37 CFR 1.84(h) because the views provided in figures 1 and 2 are not labeled separately or properly. The Notice also indicates that the figures also fail to comply with the requirements set forth in 37 CFR 1.84(l) because the line numbers and/or letters presented in Figure 2 are not uniformly thick and well-defined.

The defects noted by the Draftperson have been corrected in the Replacement Sheets that are included in the Appendix of this Amendment. More specifically, the 2 sheets of Figure 1 have been relabeled as Figures 1A and 1B, and an appropriate correction has been made to the text of the Brief Description of the Drawings which is provided in the specification. In addition, the quality of the lines, numbers, and letters presented in Figure 2 has also been improved and the text of its Brief Description has been amended to refer to panels A and B. For the Examiner's convenience, a complete set of Figures has been included in the Appendix, even though Figure 3 has not been amended. Accordingly, the Appendix contains 4 replacement sheets.

Claim Amendment(s)

In order to advance prosecution on the merits, claims 1-3 and 5 are currently amended. No new matter has been added.

Claim 1 has been amended to recite "an isolated polynucleotide consisting of a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 2, or the complement of said polynucleotide."

Claim 2 has been rewritten as an independent claim drawn to an isolated polynucleotide comprising the nucleic acid sequence of SEQ ID NO: 1.

Claim 3 has also been rewritten as an independent claim drawn to an isolated polynucleotide comprising the complement of the polynucleotide recited in claim 2.

Claim 5 has been amended to avoid recitation of fragments of the VRL-specific probes set disclosed and claimed in the instant application. More specifically, Claim 5 recites "[a] polynucleotide probe comprising an oligomer selected from the group consisting of SEQ ID NO:4-11 and 13-19 wherein said probe does not differ in sequence from a polynucleotide encoding a polypeptide of SEQ ID NO:2.

The Objections of Claims 2 and 3 Should be Withdrawn

Claims 2 and 3 are objected to as being dependent upon a rejected base claim. The Examiner indicates that these claims would be allowable if rewritten in independent form including all of the limitations of the base claims and any intervening claims.

As indicated above, Claims 2 and 3 have been rewritten in independent form, including all of the limitations of their respective base claims. Based on these amendments, Applicants respectfully request reconsideration and withdrawal of the outstanding objections.

The Rejection of Claim 5 Under 35 U.S.C. §102(b) Should be Withdrawn

Claim 5 is rejected under 35 U.S.C. §102(b) as being anticipated by Sambrook et al., Molecular Cloning, 1989. The rejection was premised on the fact that Claim 5 previously recited a fragment derived from one of the VRL-specific probes set forth in SEQ ID NOS.: 4-19. More specifically, the Examiner indicated that SEQ ID NO: 9 has a 5'-deoxythymidine, and that Sambrook *et al.*, disclose deoxythymidine which would be considered to be a fragment of SEQ ID NO: 9.

As amended, the scope of claim 5 no longer encompasses fragments of the VRL-specific probes that are provided in SEQ ID NOS: 4-11 and 13-19. Accordingly, the rejection based on the teachings of Sambrook *et al.*, has been obviated. Based on this claim amendment, Applicants respectfully request reconsideration and withdrawal of this novelty rejection.

The Rejection of Claims 1, 5 and 7-9 Under 35 U.S.C. §102(e) Should be Withdrawn

Claims 1, 5 and 7-9 were rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,444,440(Young and Ruben) (referred to herein as the '440 patent). The Examiner indicates that the '440 patent "discloses a polynucleotide encoding a polypeptide (SEQ ID NO:2) which is 100 identical to the instant SEQ ID NO:2" (Office Action, page 3). However, it is indicated that the polypeptide sequence taught by the '440 patent comprises a 126 residue-N-terminal extension relative to the VRL polypeptide that is disclosed and claimed in the instant application. Applicants note that for the record, that although the Examiner refers to the results of a sequence alignment in the Office Action, Applicants were not provided with the alignment.

Applicants respectfully traverse this novelty rejection and respectfully assert that the subject matter recited in claims 1-3, 5 and 7-9 is patentably distinct. The Examiner's attention is directed to the fact that the '440 patent claims an isolated polynucleotide

comprising a nucleic acid sequence which encodes a 888 or 889 amino acid protein which mediates intracellular calcium flux in response to thermal stimuli. However, it should be noted that there is no functional or prophetic example or express teaching indicating that a moderately high temperature (i.e., above approximately 52°C) should be used to activate the receptor.

In contrast, the instant application, discloses and claims a polynucleotide encoding a 764 amino acid Vanilloid Receptor-like (VR-L) protein which is shown to be activated by relatively high (i.e. 55°C , see page 16 and data provided in Figure 2)heat, but not to capsaicin. Furthermore, as noted by the Examiner, the disclosed polynucleotide sequence in the '440 patent comprises a different open reading frame which encodes a polypeptide that is 126 amino acids longer than SEQ ID NO:2 of the instant application.

Applicants aver that based on the disclosure provided in the '440 specification, it is unclear that a skilled artisan could either practice the invention or use the polynucleotide sequence that it discloses to express a functional VR-L receptor. This position is based on the fact that the '440 patent does not provide any guidance regarding a level of thermal stimuli (e.g., heat) that is required to activate the receptor that is disclosed and claimed therein and on certain errors in the sequences that are more fully discussed below. Therefore, it is not apparent what the teachings of the '440 patent enable.

Furthermore, as noted by the Examiner in the Office Action, the polypeptide sequence that is disclosed and claimed in the '440 patent comprises a 126 residue-N-terminal extension relative to the human consensus sequence. Therefore, it is not inherent that if an artisan were to incorporate the polynucleotide sequence disclosed and claimed in the '440 patent into an expression vector that the claimed sequence would either be expressed and/or function like a ion channel receptor, due to the presence of the N-terminal extension which would arguably interfere with the structure/function of the receptor.

A sequence comparison by pairwise SmithWaterman alignment of the genomic sequence of human chromosome 17 from basepair 16519441 to 16521650 (i.e., vanilloid receptor 2 gene) based on the latest build of the human genome and the polynucleotide sequence of the '440 patent reveals that exon 2 of SEQ ID NO: 1 of the '440 patent contains two base insertions relative to the human consensus sequence. A copy of the alignment is included as Exhibit A for the Examiners convenience. More specifically, the '440 sequence

comprises an additional T at position (-17) and (-19) relative to the A of the true ATG located at position 384 of the '440 nucleotide sequence provided in the sequence listing and Figure 1 of the '440 patent. The presence of these insertions which causes Young and Ruben to mischaracterize the open reading frame, and accounts for their description of a longer polypeptide product. It appears as if the N-terminal-extension results from translation of sequence that is actually part of the 5' untranslated region of the gene. The sequence differences present in the '440 patent, causes a frameshift which would not necessarily enable a skilled artisan to use the sequences disclosed and claimed therein to prepare an expression vector that is capable of directing the expression of a functional VR-L receptor. It should be noted that, the open reading frame of SEQ ID NO: 1 of the instant invention is identical to the consensus reference sequence provided in Exhibit A. When these factors are considered together, the '440 patent could be characterized as teaching away from the nucleotide and amino acid sequences that are disclosed and claimed in the instant application.

As amended, claim 1 now recites a polynucleotide sequence "consisting of a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 2, or the complement of said polynucleotide." It cannot be disputed that the presence of the additional T residues in the 5' untranslated region of the '440 polynucleotide causes a frameshift which results in an open reading frame that does not encode a polypeptide comprising the amino acid sequence set forth in SEQ ID NO:2 of the instant application. This is apparent from different lengths of the polypeptides encoded by the '440 polynucleotide and SEQ ID NO: 1 of the instant application, and from a comparison of SEQ ID NO:1 of the '440 patent, with SEQ ID NO:1 of the instant application and the consensus sequence of the human vanilloid receptor 2 gene. Accordingly, reconsideration and withdrawal of the novelty rejection based on U.S. Patent No. 6,444,440 are respectfully requested.

In summary, Applicants maintain that the instant claims are in condition for allowance and a favorable action on the merits is earnestly solicited.

Respectfully submitted,

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Date: 12/22/2003

Genomic sequence of chromosome 17 from 16519441 to 16521650 obtained from Ensembl (www.ensembl.org) (version 18.34.1). DNA sequence of 6,444,440 patent (SeqID 1) obtained from ABX04237 <http://srs.merck.com/srsbin/cgi-bin/wgetz?-newId+-e+[nageneseq-AccNumber:'ABX04237']>

Sequence comparison by pairwise SmithWaterman alignment. Manual addition of single-frame (6,444,440) or three-frame (genomic sequence) translation.

The sequence of the 6,444,440 sequence spans two conceptual exons, and the intron has been removed from this alignment.

Exon 1 is identical to the '440 sequence

Exon 2 contains two base differences that results in an Arg to Ala protein change (but could be the result of naturally occurring polymorphisms). It also contains a two base pair deletion as compared to the '440 sequence. This obviously results in a frame shift in the conceptual sequence, and results in STOP codons to occur in the first frame.

```
            M  V  S  L  W  W  L  A  C  P  D  R  G  E  L  S
       1 gcagatggtcagtctctggtggctagcctgtcctgacaggggagagttaa
         ||||||||||||||||||||||||||||||||||||||||||||||||||
16519441 CCAGATGGTCAGTCTCTGGTGGCTAGCCTGTCCTGACAGGGGAGAGTTAA
            M  V  S  L  W  W  L  A  C  P  D  R  G  E  L  S
             W  S  V  S  G  G  *  P  V  L  T  G  E  S  *
              G  Q  S  L  V  A  S  L  S  *  Q  G  R  V  K

          S  R  S  P  P  C  R  L  A  R  W  A  E  G  D  R
      51 gctcccgttctccaccgtgccggctggccaggtgggctgagggtgaccga
         ||||||||||||||||||||||||||||||||||||||||||||||||||
16519491 GCTCCCGTTCTCCACCGTGCCGGCTGGCCAGGTGGGCTGAGGGTGACCGA
          S  R  S  P  P  C  R  L  A  R  W  A  E  G  D  R
        A  P  V  L  H  R  A  G  W  P  G  G  L  R  V  T  E
         L  P  F  S  T  V  P  A  G  Q  V  G  *  G  *  P  R

        E  T  R  T  C  L  L  E  L  S  A  Q  S  W  G  G  R
     101 gagaccagaacctgcttgctggagcttagtgctcagagctggggagggag
         ||||||||||||||||||||||||||||||||||||||||||||||||||
16519541 GAGACCAGAACCTGCTTGCTGGAGCTTAGTGCTCAGAGCTGGGGAGGGAG
        E  T  R  T  C  L  L  E  L  S  A  Q  S  W  G  G  R
         R  P  E  P  A  C  W  S  L  V  L  R  A  G  E  G  G
          D  Q  N  L  L  A  G  A  *  C  S  E  L  G  R  E  V

         F  R  R  S  S  A  V  S  T  G  S  P  S  R  L  H  F
     151 gttccgccgctcctctgctgtcagcaccggcagcccctcccggcttcact
         |||||||||||||||||||||||| ||||||||||||||||||||||||
16519591 GTTCCGCCGCTCCTCTGCTGTCAGCGCCGGCAGCCCCTCCCGGCTTCACT
         F  R  R  S  S  A  V  S  A  G  S  P  S  R  L  H  F
          S  A  A  P  L  L  S  A  P  A  A  P  P  G  F  T
           P  P  L  L  C  C  Q  R  R  Q  P  L  P  A  S  L

          L  P  Q  P  L  L  L  R  S  S  G  I  P  A  A  A
     201 tcctcccgcagcccctgctactgagaagctccgggatcccagcagccgcc
         ||||||||||||||||||||||||||||||||||||||||||||||||||
16519641 TCCTCCCGCAGCCCCTGCTACTGAGAAGCTCCGGGATCCCAGCAGCCGCC
          L  P  Q  P  L  L  L  R  S  S  G  I  P  A  A  A
        S  S  R  S  P  C  Y  *  E  A  P  G  S  Q  Q  P  P
         P  P  A  A  P  A  T  E  K  L  R  D  P  S  S  R  H
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          T  P  W  P  Q  P  A  G
      251 acgccctggcctcagcctgcgggg    274
          |||||||||||||||||||||||||
16519691 ACGCCCTGGCCTCAGCCTGCGGGGTAA 16519714 ...intron...
          T  P  W  P  Q  P  A  G
           R  P  G  L  S  L  R  G
            A  L  A  S  A  C  G  V



            L  Q  S  G  Q  H  R  R  A  R  G  R  K  T  G  P
      275   ctccagtcaggccaacaccgacgcgcacgtgggaggaagacaggacc
            |||||||||||||||||||||||||  ||||||||||||||||||
16521443 AGGCTCCAGTCAGGCCAACACCGACGCGCAGCTGGGAGGAAGACAGGACC
            L  Q  S  G  Q  H  R  R  A  A  G  R  K  T  G  P
             S  S  Q  A  N  T  D  A  Q  L  G  G  R  Q  D  P
              P  V  R  P  T  P  T  R  S  W  E  E  D  R  T

           L  T  S  P  S  A  Q  R  S  W  L  D  R  A  M  P  P
      322 cttgacatctccatctgcacagaggtcctggctggaccgagctatgcctc
          |||||||||||||||||||||||||||||||||||||||||||| | |||||
16521490 CTTGACATCTCCATCTGCACAGAGGTCCTGGCTGGACCGAGC.A.GCCTC
           L  T  S  P  S  A  Q  R  S  W  L  D  R  A    A  S
            *  H  L  H  L  H  R  G  P  G  W  T  E  Q    P  P
          L  D  I  S  I  C  T  E  V  L  A  G  P  S  S    L  L

            P  P  R  M  T  S  P  S  S  S  P  V  F  R  L  E
      372 ctcctcctaggatgacctcaccctccagctctccagttttcaggttggag
          ||||||||||||||||||||||||||||||||||||||||||||||||||
16521538 CTCCTCCTAGGATGACCTCACCCTCCAGCTCTCCAGTTTTCAGGTTGGAG
           S  S  *  D  D  L  T  L  Q  L  S  S  F  Q  V  G  D
            P  P  R  M  T  S  P  S  S  S  P  V  F  R  L  E  T
             L  L  G  *  P  H  P  P  A  L  Q  F  S  G  W  R

          T  L  D  G  G  Q  E  D  G  S  E  A  D  R  G  K  L
      422 acattagatggaggccaagaagatggctctgaggcggacagaggaaagct
          |||||||||||||||||||||||||||||||||||||||||||||||||||
16521588 ACATTAGATGGAGGCCAAGAAGATGGCTCTGAGGCGGACAGAGGAAAGCT
            I  R  W  R  P  R  R  W  L  *  G  G  Q  R  K  A  G
             L  D  G  G  Q  E  D  G  S  E  A  D  R  G  K  L
           H  *  M  E  A  K  K  M  A  L  R  R  T  E  E  S  W

           D  F
      472 ggattttgg 480
          |||||||||
16521638 GGATTTTGG 16521646
            F  W  E
           D  F  G  S
            I  L  G
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